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Review Article

Environmental pollutants-dependent molecular pathways and carcinogenesis

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Abstract

Exposure to environmental pollutants can modulate many biological and molecular processes such as gene expression, gene repair mechanisms, hormone production and function and inflammation, resulting in adverse effects on human health including the occurrence and development of different types of cancer. Carcinogenesis is a complex and long process, taking place in multiple stages and is affected by multiple factors. Some environmental molecules are genotoxic, able to damage the DNA or to induce mutations and changes in gene expression acting as initiators of carcinogenesis. Other molecules called xenoestrogens can promote carcinogenesis by their mitogenic effects by possessing estrogenic-like activities and consequently acting as endocrine disruptors causing multiple alterations in cellular signal transduction pathways. In this review, we focus on recent research on environmental chemicals-driven molecular functions in human cancers. For this purpose, we will be discussing the case of two receptors in mediating environmental pollutants effects: the established nuclear receptor, the Aryl hydrocarbon receptor (AhR) and the emerging membrane receptor, G-protein coupled estrogen receptor 1 (GPER1).

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Keywords

environmental pollutants, genotoxic, endocrine disruptors, GPER1, AhR, carcinogenesis

1. Environmental pollutants and cancer progression

The environment presents all the elements that surround us (Schmidt 2012). In the environment, humans are exposed to pollutants in many ways, including orally, by inhalation or by the dermal route. Pollution of the environment is suspected to be one of the main causes of cancer (Parsa 2012). The process of carcinogenesis is mainly divided into three stages: initiation, promotion and progression. The initiation step follows a repeated exposure to “initiators” such as oxidative stress, chemical pollutants, virus and X-rays that increase the frequency of genetic mutations. The promotion step requires a non-mutagenic stimulus known as “promoters” such as chronic inflammation, estrogens and xenoestrogens (natural or chemical compounds that imitates estrogens) that promote proliferation of the initiated cells. The progression step comprises the expression of the malignant phenotype characterised by angiogenesis and metastasis (Liu et al. 2015). Exposure to environmental compounds may interfere at all stages of carcinogenesis, in particular at the initiation and promotion stages. Several studies have evaluated the association between widespread environmental pollutants and carcinogenesis. Indeed, epidemiological studies and *in vitro* approaches suggest that a great number of cancers could be induced *via* exposure to chemicals that humans are likely to encounter in their environment (Antwi et al. 2015, Boffetta 2006, Braun et al. 2016, Rochefort 2017, Rodgers et al. 2018, Wilde et al. 2018).

The International Agency for Research on Cancer (IARC) evaluated the carcinogenic risks to humans and has classified around 120 agents as carcinogenic, where the chemical substances represent the majority (IARC 2018). There are many kinds of environmental pollutants: 1) agriculture chemicals including pesticides such as 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (DDT); 2) the industrial chemicals including dioxins such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), metals such as arsenic compounds, plasticisers such as bisphenol A (BPA) and health care products such as phthalates; 3) the air pollutants including polycyclic aromatic hydrocarbons (PAH) such as benzo[a]pyrene (B[a]P), N-Nitrosamines such as N-Nitrosodimethylamine (NDMA), air microparticles such as sulphur dioxide and carbon monoxide; 4) drugs including exogenous hormones and 5) some natural compounds such as aflatoxines. Pollutants are characterised by their higher persistence and pervasive nature due to high lipid solubility that allows them to remain, bioaccumulate in fatty tissues and interact with the environment for a long period of time (Mathew et al. 2017). These molecules can have different mechanisms of action; they could be genotoxic or non-genotoxic which include molecules that are able to induce epigenetic modifications, to alter the endocrine system, to act as immunosuppressors or inducers of tissue-specific toxicity and inflammatory responses (Caldwell 2012, Hernández

et al. 2009). In this review, we will be discussing mainly the genotoxic compounds and the endocrine disruptors.

A "genotoxic" agent is able to damage the genetic material by inducing DNA damage, mutation or both (Hayashi 1992). Genotoxicity is a key feature of carcinogenesis; it promotes chromosome changes that may be structural (such as translocations, deletions, insertions, inversions, micro-nuclei and changes in telomere length) or numerical, affecting the numbers of chromosomes as in the case of aneuploidy and polyploidy (Smith et al. 2016). Genotoxicity, due to environmental molecules, can alter the oncogenes and tumour suppressor genes that regulate processes such as cell proliferation, cell death, cell differentiation and genomic stability (Hanahan and Weinberg 2011).

Endocrine disruptors or endocrine disrupting chemicals (EDC) are pseudo-persistent compounds present in the environment at very low concentrations; however, these low levels are able to interfere with hormonal regulation pathways causing effects leading to a variety of health problems, such as cancer, specifically the hormone-dependent type (breast, ovarian, endometrial, prostate, testicular) (Abaci et al. 2009, Nohynek et al. 2013, Rachoń 2015, Rochefort 2017). Endocrine disruptors act directly with hormone receptors by imitating or preventing the action of natural hormones (Schug et al. 2016). Most of these compounds have structures similar to steroid hormones such as estrogen and could interfere with the action of this hormone through binding to estrogen receptors (ER) (Shanle and Xu 2011, Tilghman et al. 2010). It is important to mention that estrogens activate different signalling pathways known to play an important role in tumour development (Vrtačnik et al. 2014).

In Table 1, we listed some of the main environmental genotoxic molecules or endocrine disruptors that are known/thought to be implicated in the process of carcinogenesis.

Table 1.

List of the most common environmental molecules (genotoxics and endocrine disruptors) and the different types of cancers developed following their exposure.

Class	Source	Compound	Mechanism of action	Target organs	References
N-Nitrosamines	Contaminated water, Preserved foods, Tobacco smoke	N-Nitrosodimethylamine (NDMA)	Genotoxic	Liver	Beebe et al. 1993, Tsutsumi et al. 1993
				Esophagus (squamous cell carcinoma)	Keszei et al. 2013
		N-Butyl-N-(4-hydroxybutyl)nitrosamine (BBN)	Genotoxic	Bladder	Chuang et al. 2014, Parada et al. 2012, Sagara et al. 2010

Polycyclic Aromatic Hydrocarbon (PAH)	Grilled meat, Tobacco smoke, Combustion of organic substances	2-Acetylaminofluorene (2-AAF)	Genotoxic	Liver	Gauttier et al. 2013, Pogribny et al. 2009, Sehrawat and Sultana 2006
		7,12-Dimethylbenz [a]anthracene (DMBA)	Genotoxic	Breast	Siddiqui et al. 2013, Wang et al. 2011
				Mouth (Buccal cheek pouch)	Mang et al. 2006
		Benzo[a]pyrene (B[a]P)	Genotoxic	Lung	Anandakumar et al. 2008a, Anandakumar et al. 2008b
				Stomach	Goyal et al. 2010
				Colon	Diggs et al. 2013
Compounds of natural origin	*Aspergillus flavus*, *Aspergillus parasitus*	Aflatoxines	Genotoxic	Liver	Johnson et al. 2014, Liu et al. 2011
	Aristolochia clematitis	Aristolochic acid	Genotoxic	Urethra	Gruia et al. 2015
Pesticides	Insecticides, Acaricides	1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (DDT)	Endocrine disruptors	Breast	Cohn et al. 2007
				Liver	McGlynn et al. 2006
Plasticiser	Plastic products, Epoxy resin	Bisphenol A (BPA)	Endocrine disruptors	Breast	Castillo Sanchez et al. 2016, Lei et al. 2017, Mandrup et al. 2016, Xu et al. 2017, Zhang et al. 2015, Zhang et al. 2016
				Cervical	Ma et al. 2015
				Prostate	Prins et al. 2014
				Ovaries	Kim et al. 2015
				Lung	Zhang et al. 2014
				Larynx	Li et al. 2017
Dioxin	Formed during industrial process, present in dust, soil and water	2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)	Endocrine disruptors	Lung	Chen et al. 2014
Phthalates	Plastics products, Perfumes, Cosmetics and Care products	Di-n-butyl phthalate (DBP)	Endocrine disruptors	Breast	Chen and Chien 2014, Hsieh et al. 2012
		Mono-2-ethylhexyl phthalate (MEHP)	Endocrine disruptors	Ovaries	Chang et al. 2017

2. Receptors targeted by environmental pollutants

Previous studies have suggested that environmental factors are able to induce deleterious effects within the cells through the activation of cellular receptors (Mnif et al. 2007, Routledge et al. 2000, Shi et al. 2009). It is important to note that the interactions between most of the environmental pollutants and their receptors are implicated in the regulation of molecular pathways involved in cancer progression, such as proliferation, metabolism of xenobiotics and apoptosis (Burz et al. 2009, Duronio and Xiong 2013, Rushmore and Kong 2002). It is known that environmental molecules, such as TCDD, B[a]P, BPA and phthalates, have the ability to interact with the two types of cellular receptors: nuclear and membrane receptors (Delfosse et al. 2014, Thomas and Dong 2006, Wallace and Redinbo 2013). Most of the exogenous agents act either as receptor's agonists or antagonists and compete with endogenous ligands to bind to their receptors (Handschin and Meyer 2003, Schlyer and Horuk 2006, Venkatakrishnan et al. 2013, Wang and LeCluyse 2003). In general, the effects of these interactions are able to induce two types of mechanisms: 1) the activation of cell surface receptors that induce signal transduction pathways leading to various physiological and pathological processes and playing important roles in cancer biology (Kampen 2011, Pierce et al. 2002); 2) an intracellular activation mediated by nuclear receptors acting as transcription factors in the nucleus resulting in modifications in the expression of several genes including enzymes involved in the metabolism of the exogenous molecules (Delfosse et al. 2014, Sever and Glass 2013).

2.1. Nuclear receptors

Nuclear receptors are activated by both intracellular and extracellular signals and act as transcription factors of target genes (Sever and Glass 2013). Many of these target genes are involved in cell growth and cell differentiation, development and metabolism (Carlberg and Seuter 2010, Kininis and Kraus 2008). There are three most common sub-families of nuclear receptors: 1) the classical steroid hormone receptors or endocrine receptors that bind to a unique high affinity ligand such as estrogens, androgens, glucocorticoids, thyroxin, progesterone, mineralocorticoids etc. and exert a wide range of biological functions including cell homeostasis, differentiation, regulation of proliferation, survival and cell death (Ward and Weigel 2009). Both the endogenous ligands (hormones) and the hormone receptors are targeted by environmental chemicals. For instance, the drug prulifloxacin activates the androgen receptor, while BPA and dicyclohexyl phthalate activate the glucocorticoid receptor (Lynch et al. 2017, Sargis et al. 2010). The classical nuclear ER, ERα and ERβ, are the most sensitive receptors to be targeted by some EDC that will compete with endogenous estrogen and target directly ER. EDC includes the pharmaceutical chemicals diethylstilbestrol, BPA, DDT and phytoestrogens such as genistein (Chen et al. 2018, Shanle and Xu 2011). 2) Orphan receptors, called as such because of their unknown physiological ligands, but represent candidate receptors for new ligands or hormones; they play important roles in cellular homeostasis and diseases including cancer where over- or under-expression of some receptors have prognostic significance for patient survival (Aesoy et al. 2015, Hummasti and Tontonoz 2008, Safe et

al. 2014). 3) The xenobiotic receptors which are the most important group of nuclear receptors towards environmental molecules (Li and Wang 2010). They play an important role in cellular responses to accumulated endotoxins, chemicals compounds and their metabolites (Li and Wang 2010). To date, studies are focusing on three main xenobiotic receptors: the constitutive androstane receptor, the pregnane X receptor and the aryl hydrocarbon receptor (AhR), because of their predominance in the regulation of hepatic responses either to drugs or to environmental chemicals, such as some PAH and dioxin compounds (Banerjee et al. 2015, Verma et al. 2017, Vondráček and Machala 2016). Xenobiotic receptors play an important role between the environment and the physiological mechanisms due to their involvement in the transcriptional regulation of cytochromes P450 (CYP) family which represents one of the most important and predominant enzyme superfamilies involved in metabolism of xenobiotics; however, in some cases this metabolic transformation of xenobiotics may also produce active metabolites, able to induce DNA adducts and mutations or toxic intermediates (Fujii-Kuriyama and Mimura 2005, Guéguen et al. 2006, Tolson and Wang 2010). In addition, these three xenobiotic receptors are known to regulate, at the transcriptional level, the ridine 5'-diphospho-glucuronosyltransferase which is an enzyme involved in the detoxification process and the ATP-binding cassette sub-family G member 2 Breast Cancer Resistance Protein frequently associated with therapy resistance in cancers (Jigorel et al. 2006, Spitzwieser et al. 2016, Sugatani et al. 2001, Tompkins et al. 2010).

2.2. Membrane receptors

Membrane receptors are transmembrane proteins that serve as a communication interface between cells and their external and internal environments (Pierce et al. 2002, Venkatakrishnan et al. 2013). Three major classes of membrane receptors exist: 1) the enzyme linked-receptors that lack intrinsic catalytic activity and dimerise after binding with their ligands, in order to activate downstream signal transductions pathways through one or more cytosolic protein-tyrosine kinase (i.e. human growth factor receptors) (Dudek 2007); 2) the channel-linked receptors (also called ligand-gated ion channels) where the ligand binding changes the conformation of the receptor; in this case, specific ions flow through the channel altering the electric potential across the membrane of the target cell (Absalom et al. 2004); and 3) the G-protein coupled receptors (GPCRs).

GPCRs represent one of the largest and most diverse families of membrane proteins. They are encoded by more than 800 genes and constitute the largest class of drug targets in the human genome (Ghosh et al. 2015, Venkatakrishnan et al. 2013). After ligand binding, GPCR undergo conformational changes; they couple to and activate a G protein, then trigger a cascade of signal transduction leading to various physiological and pathological processes (Venkatakrishnan et al. 2013). GPCRs are also targeted by environmental pollutants, such as TCDD which was identified to activate the GPCR signalling pathway maps (Jennen et al. 2011). In endothelial cells and adipocytes, B[a]P is able to bind the beta(2)-adrenergic receptor (β2ADR), a subfamily of GPCRs and induce intracellular calcium mobilisation and lipolysis (Irigaray et al. 2006, Mayati et al. 2012). GPCRs can also be targeted by endocrine disruptors. Indeed, some phthalate esters have the potential to

bind to the G protein-coupled cannabinoid-1 (CB1) receptor and to modify CB1 receptor-dependent behaviour; DDT acted as a positive allosteric modulator on the human follitropin receptor function (Bisset et al. 2011, Munier et al. 2016).

GPCRs are involved in many diseases including cancer (Nohata et al. 2017, Schlyer and Horuk 2006). A known GPCR, involved in the activation of intracellular signalling pathways that promote cancer development, is the G protein-coupled estrogen receptor 1 (GPER1), also known as GPR30, which is largely localised within intracellular membranes predominantly in the endoplasmic reticulum, while also found weakly expressed at the cell surface membrane (Cheng et al. 2011, Gaudet et al. 2015). GPER1 is activated by a large range of stimuli, including hormones and environmental molecules (Lu and Wu 2016). This receptor is characterised by its involvement in the estrogen signalling pathway and its high affinity to xenoestrogens and 17β-estradiol (E2), especially in cells that do not express classical ER (Filardo et al. 2000, Maggiolini and Picard 2010, Prossnitz and Hathaway 2015).

The present review will highlight the recent research advances regarding carcinogenic mechanisms with the focus on two receptors in mediating environmental pollutants effects: the established nuclear receptor the Aryl hydrocarbon receptor (AhR), known to have a major role in the metabolism of toxic compounds and the promotion of tumours and the emerging membrane receptor G-protein coupled estrogen receptor 1 (GPER1), known to mediate estrogenic activity of environmental xeno-estrogens in different cell types (Filardo 2018, Xue et al. 2018).

3. The case of AhR, an established nuclear receptor in mediating environmental pollutants effects

3.1. Overview

AhR is a cytosolic nuclear receptor that, after binding with its ligand, moves to the nucleus and acts as a transcription factor (Denison et al. 2002, Schmidt and Bradfield 1996). It belongs to the family of basic-helix/loop/helix per-Arnt-sim (bHLH/PAS) domain containing transcription factors (Burbach et al. 1992, Fukunaga et al. 1995). The structure of AhR is composed of an amino (N-) terminal bHLH domain, which is a common entity in a variety of transcription factors, required for DNA binding; followed by two per-Arnt-sim (PAS) domains (A and B) and a carboxy (C-)terminal transactivation domain (TAD) (Crews and Fan 1999, Fukunaga et al. 1995, Jones 2004). The ligand binding site of AhR is present within the PAS-B domain (Burbach et al. 1992, Coumailleau et al. 1995). In the absence of ligand, AhR is sequestered in the cytoplasm by the heat shock protein 90 (Hsp90), hepatitis B virus x-associated protein 2 (XAP2) and the p23 protein. Activation by a ligand induces the dissociation of XAP2 and p23; and the AhR/Hsp90 complex translocates to the nucleus forming the first essential step in AhR activation (Ikuta et al. 2000, Kazlauskas et al. 2001, Tsuji et al. 2014). Once in the nucleus, the AhR detaches from Hsp90 and heterodimerises with AhR nuclear translocator (ARNT), allowing the AhR/ARNT complex to bind to

response elements called xenobiotic responsive elements (XRE), located in the promoters of target genes to induce their transcription (Dolwick et al. 1993, Fukunaga et al. 1995). It has been shown that AhR activation can cause toxic and carcinogenic effects (Schmidt and Bradfield 1996). Many metabolites could be candidates for natural endogenous AhR ligands such as the arachidonic acid metabolites (i.e. the lipoxin A4), heme metabolites (i.e. the bilirubin) and the tryptophan metabolites (i.e. the kynurenine and the kynurenic acid) (Schaldach et al. 1999, Sinal and Bend 1997, Wirthgen and Hoeflich 2015). The best-characterised AhR ligands that act as powerful activators have been identified as environmental toxins (Denison and Nagy 2003). These activators derive mainly from two classes of compounds: PAH such as B[a]P and halogenated aromatic hydrocarbons such as TCDD which have high-affinity for AhR binding (Denison et al. 2002). It has been proven that B[a]P induced its carcinogenicity at least via AhR (Shimizu et al. 2000). During its activation, AhR stimulates the expression of target genes, such as CYP1A1, CYP1A2 and CYP1B1, that are important in the metabolism and bioactivation of carcinogens (Kerzee and Ramos 2001, Oyama et al. 2012).

3.2. AhR and cancer

Constitutive activation of AhR. Studies have shown that AhR can be constitutively active, presumably because of endogenous ligands and plays an important role in the biology of several cell types when exogenous ligands (environmental molecules) are absent. Schlezinger et al. (2006) reviewed the involvement of AhR in the mammary gland tumourigenesis by inhibiting apoptosis while promoting the transition to an invasive phenotype. Additionally, in a human hepatoblastoma cell line, Terashima et al. (2013) demonstrated that, under glucose deprivation, the AhR pathway induces vascular endothelial growth factor (VEGF) expression by activating transcription factor 4. In addition, knockdown or inhibition of AhR inhibits the invasion and migration of cancer cells, as well as downregulates the expression of metastasis-associated genes and tumour cells (Goode et al. 2014, Parks et al. 2014). *In vivo* and *in vitro*, D'Amato and his colleagues demonstrated that the tryptophan 2,3-dioxygenase (TDO2)-AhR pathway plays a crucial role in the anoikis resistance and metastasis of triple negatif breast cancer (TNBC) cell lines. TNBC cells regulate the enzyme TDO2, thereby causing AhR activation by this endogenous ligand kynurenine catalysed by TDO2 (D'Amato et al. 2015). Moreover, in a human breast cancer cell line MDA-MB-231, knockdown of AhR by RNAi decreased proliferation, anchorage-independent growth and migration of the cells, suggesting a pro-oncogenic function of AhR (Goode et al. 2013).

Environmental molecules that deregulate cell cycle control via AhR pathway. As cited previously, the TCDD and B[a]P represent high-affinity xenobiotic ligands for the AhR. Emerging evidence has demonstrated the role of the AhR and its ligands in cancer. A study showed that the treatment of rat liver normal cells with TCDD leads to the activation of the transcription factor JUN-D, *via* AhR, resulting in the transcriptional induction of the cell cycle regulator proto-oncogene *Cyclin A*, that provokes a release from contact inhibition (Weiss et al. 2008). Within the same cell lines, the B[a]P, also *via* AhR, disrupts the contact inhibition and enhances cell proliferation (Andrysík et al. 2007). Studies in a human

adenocarcinoma cell line revealed that AhR agonist (TCDD) was able to stimulate the growth of cancer cells by inducing the expression of E2F/DP2 complex which is involved in cell cycle regulation and DNA synthesis (Shimba et al. 2002). Thus, the activation of AhR plays a significant role in cell cycle deregulation induced by environmental molecules.

Environmental molecules that influence apoptosis. Inhibition of apoptosis is also a factor for tumour promotion/progression. In a model for studying hepatocarcinogenesis, TCDD stimulates the clonal expansion of pre-neoplastic hepatocytes by inhibiting apoptosis (Bock and Köhle 2005). It was also demonstrated *in vitro* that the use of AhR antagonist abolishes resistance to TCDD-induced apoptosis in three different lymphoma cell lines. Indeed, the TCDD-mediated inhibition of apoptosis *via* AhR was associated with an increase in cyclooxygenase-2 (COX-2) and deregulation of genes of the B-cell lymphoma-2 (*Bcl-2*) family such as the anti-apoptotic proteins Bcl-xl and Mcl-1 (Vogel et al. 2007). In addition, the activation of AhR by TCDD in mouse fibroblasts represses the induction of the pro-apoptotic E2F1 target genes such as *TP73* and Apoptotic protease activating factor 1 *(Apaf1)*; however, the inhibition of AhR causes an increase in E2F1 protein that will promote apoptosis (Marlowe et al. 2008). Moreover, Bekki *et al*. explored the activation of AhR by TCDD and kynurenine (an endogenous ligand for AhR) and found that these compounds were able to suppress the apoptotic response induced by anti-cancer therapy in breast cancer cells and induce inflammatory genes, such as *COX-2* and nuclear factor kappa-light-chain-enhancer of activated B cells subunit RelB (*NF-κB*) (Bekki et al. 2015). These studies showed an anti-apoptotic function of the AhR suggesting its tumour promoting role.

Environmental molecules that affect cellular plasticity. Deregulation of cell–cell contact and tumour malignancy is associated with increased AhR expression. For instance, Diry et al. (2006) highlighted the effect of TCDD and 3-methylcholanthrene *via* AhR on cellular motility. Dioxin stimulated cytoskeleton remodelling, resulting in an increased interaction with the extracellular matrix and loosening of the cell-cell contact. This pro-migratory activity was mediated by the activation of Jun NH2-terminal kinase (JNK) and reverted with a JNK inhibitor (Diry et al. 2006). Additionally, Andrysík et al. (2013) demonstrated that the AhR agonist TCDD was able to disrupt contact inhibition and reduce gap junctional intercellular communication *via* downregulation of connexin-43 in an AhR-dependent manner. In addition, activation of B[a]P-dependent signal transduction pathway, where AhR involvement is primordial in B[a]P-induced carcinogenesis, also interferes with biological processes involved in migration and invasion of breast cancer cells and Triple Negative Breast Cancer (TNBC) cells which represents the worse prognosis sub-type in breast cancer (Castillo-Sanchez et al. 2013, Guo et al. 2015, Novikov et al. 2016, Shimizu et al. 2000).

Environmental molecules that are able to induce DNA damage leading to genetic mutations. It is well known that the environmental molecule B[a]P induces, *via* AhR, the expression of CYP1A1, which is involved in the biotransformation of B[a]P, a procarcinogen, into B[a]P-diol-epoxide (BPDE), an ultimate mutagen with a strong electrophilic power that allows it to form DNA adducts that cause cytogenetic alterations,

DNA breaks, DNA damage and mutations in oncogenes and tumour suppressor genes (Chiang and Tsou 2009, IARC 2012, Morris and Seifter 1992, Rundle et al. 2000, Tarantini et al. 2011). BPDE was demonstrated to induce *K-ras* mutations in normal human bronchial epithelial and fibroblast cells; these mutations have also been found in lung tumours of people exposed to the smoke of charcoal combustion during their work (Feng et al. 2002, IARC 2010).

AhR activity maintains cancer stem cells (CSC) capacity. AhR has also been reported to affect CSC, a subtype of cancerous cells and to lead to the initiation, progression and development of metastases in the carcinogenesis (Gasiewicz et al. 2017). One hypothesis assumes that tumours are maintained by a self-renewing CSC population, which is also able to differentiate into non-self-renewing cells populations that make the mass of the tumour (McDermott and Wicha 2010). Stanford et al. (2016) have shown that activation of AhR increases the development of CSC and their characteristics in TNBC cells. Furthermore, hyperactivation of AhR by B[a]P increases the activity of the stem cells specific marker, the aldehyde dehydrogenase (ALDH) and the expression of migration/invasion-associated genes such as *Snai1*, *Twist 1*, *Twist2*, *Tgfb1* and *Vim.* In addition, AhR ligands increase the translocation of the sex-determining region Y-box 2, a master regulator of self-renewal, to the nucleus (Stanford et al. 2016). These data highlight the role of AhR in the development of cells with cancer stem cell-like properties and mostly the role of environmental AhR ligands in intensifying breast cancer progression. A recent study demonstrated that the AhR/CYP1A1 signalling pathway, activated by TCDD and 2,4-dimethoxybenzaldehyde, appears to be involved in the regulation (development, maintenance and self-renewal) of breast CSC *via* PTEN/Akt and β-catenin pathways by inhibiting the expression of PTEN and activating the expression of Akt and β-catenin (Al-Dhfyan et al. 2017).

The possible AhR biomarker value in cancer. Few studies investigated the prognosis value of AhR in cancer. In upper urinary tract tumours, the high levels of nuclear AhR expression predicted a higher tumour grade (Ishida et al. 2010). Later, it has been explored that nuclear translocation of AhR was associated with a poor prognosis in squamous cell carcinoma (Su et al. 2013). Moreover, ERα negative breast cancers exhibited a high expression of AhR, coupled with hypermethylation of the CpG islands of the *BRCA1* gene promoter (or in other words with *BRCA1* inactivation), suggesting that it could serve as a predictive biomarker for tumour development (Romagnolo et al. 2015). Finally, a recent study suggested the use of Memo-1, an important effector of cell migration mediated by AhR activation, as a new prognostic factor of aggressive disease in colorectal cancer patients (Bogoevska et al. 2017). Finally, Roth et al. (2009) demonstrated that AhR expression was higher in patients with a family history of upper gastrointestinal cancer exposed to PAH, revealing the deleterious effects of PAH exposure, including PAH-induced cancer.

The molecular mechanisms affected by the activation of AhR by environmental pollutants, discussed above, are represented in Fig. 1.

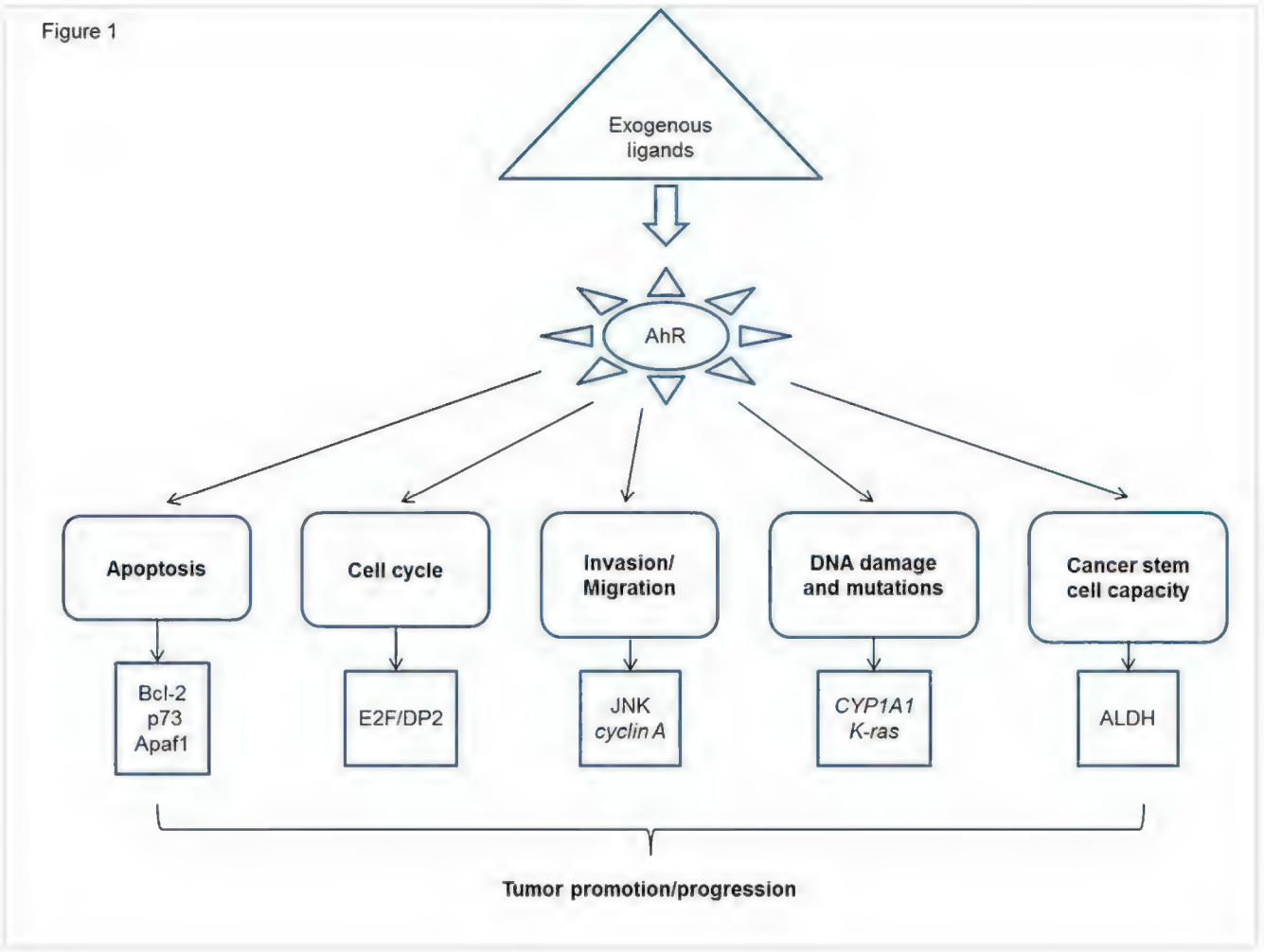

Figure 1.

Schematic resume representing the main effects of environmental pollutants in carcinogenesis mediated by the AhR receptor. Exogenous ligands activate AhR and affect several molecular mechanisms resulting in various genes expression that cooperate to promote carcinogenesis.

4. The case of GPER1, an emerging receptor in mediating environmental pollutants impact

4.1 Overview

GPER1 is a seven transmembrane-domain G protein-coupled receptor that shares, with other GPCR, a similar global architecture which consists of a transmembrane canonical part formed of seven helices α with various sequences serving as a communication link between the ligands and the G protein coupling region; the extracellular part consists of three extracellular loops containing the N-terminus and the intracellular part consisting of three intracellular loops with the C-terminus (Lu and Wu 2016). A large number of molecules that bind to classical ER can also bind to GPER1. Amongst these ligands, we distinguish some molecules that bind strongly to GPER1 such as: 1) the endogenous ligands including E2 acting as agonist and estriol (E3) acting as antagonist; 2) the anti-estrogens tamoxifen and ICI 182,780 used in hormone therapy, in contrast to their antagonistic properties on ER, act as agonists on GPER1; and 3) the xeno-estrogens such

as DDT, mono-2-ethylhexyl phthalate (MEHP) and BPA (Fitzgerald et al. 2015, Lappano et al. 2010, Thomas et al. 2005, Thomas and Dong 2006, Tiemann 2008). The localisation of GPER1 in the membrane promotes this coupling with heterotrimeric G proteins composed of Gαs and Gβ/γ subunits (Maggiolini and Picard 2010, Thomas et al. 2005), following the activation of GPER1 by a ligand, localised on the membrane of endoplasmic reticulum. It adopts a conformational change resulting in an exchange of guanosine diphosphate by guanosine triphosphate at the level of the G protein and which in turn triggers the dissociation of the α subunit from the β/γ subunits and from the receptor. The Gβ/γ subunits stimulate Src tyrosine kinase leading to the activation of matrix metalloproteinases (MMP) and therefore triggering a series of intracellular signal transduction cascades comprising the epidermal growth factor receptor (EGFR), a plasma membrane-associated enzyme which belongs to the ErbB/HER family of tyrosine kinase receptors (Filardo et al. 2000, Maggiolini and Picard 2010, Quinn et al. 2009). The MMP will then release heparin-bound EGF (HB-EGF) from the cell surface; EGF binds to its receptor, the EGFR and thus activates the underlying signalling pathways such as the PI3K/Akt pathway and MAPK/ERK pathway in normal and malignant cells (Fan et al. 2018, Maggiolini and Picard 2010). As for the subunit Gαs, it will activate the adenylyl cyclase and then produce cAMP that in turn activates the phospholipase C (Maggiolini and Picard 2010).

4.2. GPER1 and cancer

GPER1 may promote carcinogenesis. The chemical structure of BPA that looks like E2 provides estrogenic properties to BPA (Brzozowski et al. 1997). It was demonstrated that, besides its activity through ER, BPA induces cell proliferation and migration *via* the GPER1/EGFR/ERK pathway in breast cancer cells (Pupo et al. 2012). In addition, the fact that BPA is able to bind GPER1 and to activate non-genomic pathways could explain these fast effects on the activation of signalling pathways, even at low doses (Richter et al. 2007, Talsness et al. 2009). For instance, at doses of 10^{-9} M to 10^{-12} M, BPA showed a proliferative effect on testicular cancer cells JKT-1 by activating the signalling pathways involving the protein kinase A and protein kinase G *via* GPER1 (Bouskine et al. 2009). Moreover, in seminoma cells, BPA was also able to promote proliferation through GPER1 (Chevalier et al. 2011). By binding to GPER1, BPA induced activation of ERK1/2 and transcriptional regulation of *c-fos* in human breast cancer cells *via* the AP1-mediated pathway (Dong et al. 2011). Additionally in breast cancer cells and through GPER1, BPA activated signal transduction pathways; it mediated migration and invasion by inducing the expression of kinases such as FAK, Src and ERK2 and by increasing AP-1 and NFκB-DNA binding activity through a Src- and ERK2-dependent pathway (Castillo Sanchez et al. 2016). Interestingly, in non-hormonal cancers, BPA binds to GPER1 and induces cancer progression in laryngeal squamous cell carcinoma and lung cancer cells (Li et al. 2017, Zhang et al. 2014). In a hypoxic microenvironment, BPA stimulated cell proliferation and migration of vascular endothelial cells and breast cancer cells *in vitro* by up-regulating the hypoxia inducible factor-1 alpha and VEGF expressions in a GPER1-dependent manner; and enhanced tumour growth *in vivo* (Xu et al. 2017). A recent study showed that one of the BPA derivatives, 4,4'-thiodiphenol, displaying more powerful estrogenic activity than BPA, was able to stimulate cell proliferation in ERα positive cancer cells by activating the

GPER1-PI3K/AKT and ERK1/2 pathways (Lei et al. 2017). Therefore, more attention should be paid to BPA exposure. In addition, lower concentrations of phthalates were able to promote human breast cancer progression by inducing a proliferative effect through the PI3K/AKT signalling pathway (Chen and Chien 2014). Recent data showed that the MEHP, an environmental xenoestrogen, triggered the proliferation of cervical cancer cells within a GPER1/Akt-dependent-manner by directly binding to GPER1 (Yang et al. 2018). As for DDT, in 2006 Thomas and Dong showed that the derivative compounds of DDT displayed affinity for GPER1, but to date, data lack studies for testing the effect of DDT on carcinogenesis *via* the GPER1-dependent manner (Thomas and Dong 2006).

GPER1 is implicated in pathways that lead to the activation of the transcriptional machinery. Studies have demonstrated the involvement of GPER1 in cell proliferation, cell survival and cell migration mechanisms by inducing the transcription of genes such as *cyclin D2, Bcl-2*, connective tissue growth factor *(CTGF)* and the oncogene *c-fos* etc. (Kanda and Watanabe 2003, Kanda and Watanabe 2004, Maggiolini et al. 2004, Pandey et al. 2009). These data suggest possible roles for GPER1 in the development of metastases and in the resistance to anti-estrogens. The role of GPER1 in promoting cancer is also reinforced with the presence of a cross talk between GPER1 and the insulin-like growth factor receptor-1 which is associated with multiple tumour progression characteristics, such as the development of metastases and resistance to chemotherapy by triggering downstream pathways, such as ERK and AKT (De Marco et al. 2013, Knowlden et al. 2008, Lappano et al. 2013).

The possible GPER1 biomarker value in cancer. Several studies have highlighted the use of GPER1 as a cancer biomarker. The results of a clinical study showed that the expression of GPER-1 might correlate with clinical and pathological-poor outcome biomarkers, by showing an association with metastasis, human epidermal growth factor receptor 2 (HER2) expression and tumour size (Filardo et al. 2006). GPER1 has also been shown to be an important prognostic factor in high-risk endometrial cancer patients with lower survival rates (Smith et al. 2007). High expression levels of GPER1 have been correlated with low survival rates in breast cancer patients treated with tamoxifen and in patients with the aggressive epithelial ovarian cancer (Ignatov et al. 2011, Smith et al. 2009). *In silico*, a bad prognostic value for high levels of expression of GPER1 in HER2+ breast cancers subtype was obtained (Yang and Shao 2016). As well, Fahlén et al. (2016) have found that malignant breast tumours showed a high expression of GPER1 compared to benign tumours. Interestingly, a recent study showed that GPR30 expression was observed in both the cytoplasm and nucleus of cells from ovarian cancer tissues where the nuclear GPER1 expression predicts poor survival in patients with ovarian cancer, especially in those with a high grade malignancy (Zhu et al. 2018). To date, there is no study showing a correlation between the environmental carcinogen exposure and GPER1 expression to be used as a biomarker.

The molecular mechanisms affected by the activation of GPER1 by environmental pollutants, discussed above, are represented in Fig. 2.

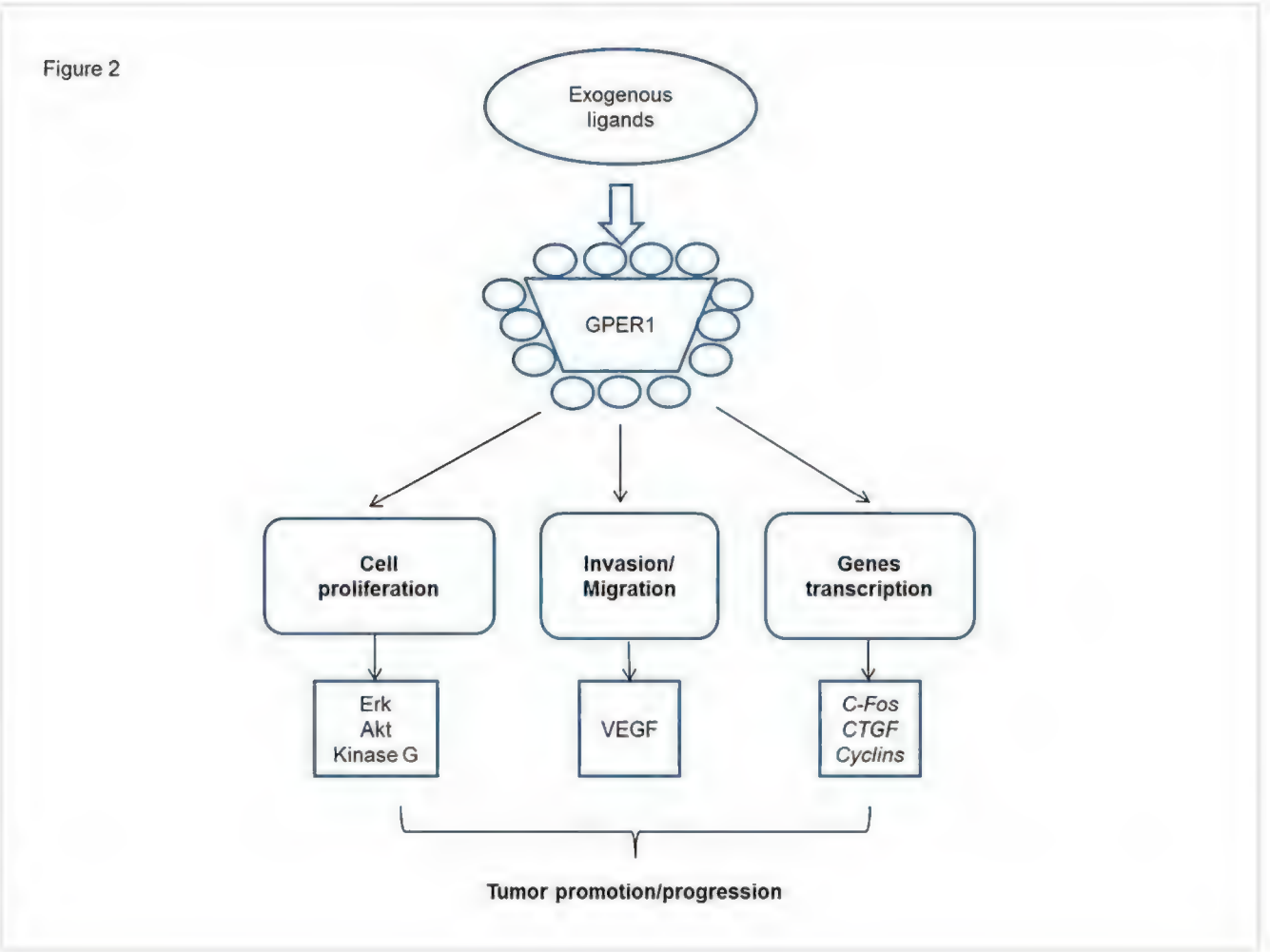

Figure 2.

Schematic resume representing the main effects of environmental pollutants in carcinogenesis mediated by GPER1 receptor. Exogenous ligands activate GPER1 and affect several molecular mechanisms resulting in various genes expression that cooperate to promote carcinogenesis.

5. Conclusion

Several risk factors were identified playing important roles in carcinogenesis. Some major factors were attributed to the exposure to environmental molecules. In this review, we showed that exposure to environmental molecules can play a crucial role in the process of carcinogenesis. These molecules have the ability to interact with cellular receptors and act as either initiators of carcinogenesis by their genotoxic effect or agents promoting carcinogenesis *via* their estrogenic-like activities (xenoestrogens). Amongst cellular receptors, we highlighted two main receptors AhR and GPER1, where many studies demonstrated their implication in carcinogenesis. As discussed, studies reported that environmental pollutants exert estrogenic effects. The established nuclear receptor AhR, has long been identified as a receptor that mediates environmental pollutants effects. Acting as a transcription factor that responds to xenobiotics and play significant roles in the development and progression of cancer cells such as proliferation and differentiation, genetic damage, toxins metabolism, angiogenesis and survival, where its overexpression and constitutive activation have been observed in various tumour types. Some studies have also suggested that higher AhR activity could be correlated with increased

aggressiveness and a poor prognosis. Previously, mechanistic studies focused on their actions mediated by the ER pathway and gave less importance to their effects mediated by the GPER1 pathway. However, GPER1 proved to be an emerging membrane receptor in mediating environmental pollutants impact. The currently available data suggest that GPER1 is a potential target for xenoestrogens in the human body. There is now good evidence that GPER1 may contribute separately to estrogen-induced carcinogenesis due to its ability to activate transcriptional machinery and employ different intracellular signalling mechanisms that promote cancer progression such as cell proliferation, migration, escape from apoptosis and cell cycle arrest. Moreover, several studies do suggest that GPER1 measurement alone may be a significant biomarker in cancer and therefore may hold a prognostic significance.

In this context, more studies are needed to fully establish the role of pollutants that we are chronically (daily) exposed to, in inducing carcinogenesis and to develop a better understanding of how cellular receptors cooperate with these molecules to drive the biology of cancer. In fact, this type of research encounters important barriers to progress; for instance, some chemicals are rapidly metabolised, many exposures are complex mixtures of chemicals that have varied mechanisms of action, thus, there is a great challenge to reconstruct environmental exposures to assess pollutants effects. Furthermore, research needs to include continued support of cohorts with prospective exposure measurements from early life, so that further follow-ups would be informative. Finally, epidemiological studies highlight the need for better chemical testing and risk assessment approaches that are relevant to cancer that could be essential for cancer prediction and prevention. Clearly, the current scientific challenge is to identify new molecular biomarkers for environmental exposure that could be used to develop candidate prevention strategies for the environmental carcinogenesis induced by molecules with different mechanisms of action.

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Author contributions

SEG planned the different sections, edited and corrected the review. MEH wrote and edited the review. PC and MDA corrected the review.

Conflicts of interest

No conflict of interest to declare.

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